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Disease-a-Month

Chemoprophylaxis of Infectious Diseases (Part III)

MAXWELL FINLAND

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Maxwell Finland—CHEMOPROPHYLAXIS OF INFECTIOUS DISEASES (PART III)

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Chemoprophylaxis of Infectious Diseases

III. Applications in Surgical and Obstetric Practice; General Discussion and Summary

MAXWELL FINLAND

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Part I of this three-part series appeared as the December 1959 issue. It dealt with general considerations of chemoprophylaxis and its application to streptococcal infections, rheumatic fever, glomerulonephritis and bacterial endocarditis.

Part II appeared as the July 1960 issue and dealt with other applications in general medicine and pediatrics.

CHEMOPROPHYLAXIS IN SURGERY

NEARLY all surgeons who have had extensive experience with infections in surgery and have studied the problem agree that the routine use of antibacterial agents in "clean" operations is not indicated; many of them consider it undesirable, and a few believe it is dangerous (1–9). Nevertheless, the number of exceptions in specific situations makes an imposing list of major (and many minor) surgical operations for which they consider antibiotic prophylaxis to be desirable or useful. Nearly all agree that antibiotics should be used in operations through infected areas of the gastrointestinal, respiratory and genitourinary tracts. This is often broadened to include the entire field of oral surgery, except for minor procedures or operations in the healthy mouth (10), and all operations on the alimentary canal, although some would specifically exclude elective operations on the stomach for peptic ulcers (4). Prophylactic drugs are often recommended whenever a catheter is required for bladder drainage, even though the urine is originally not infected, and, in fact, in any operation involving the urinary tract (2, 8).

Extension of chemoprophylaxis to certain clean operations has been generally recommended and justified either because

infections in the areas involved are particularly serious or because the operations may be prolonged and thus liable to contamination. Neurosurgical operations, open-heart surgery, operations on blood vessels and orthopedic operations would be included in this category, especially if they involve insertion of foreign bodies. Antibacterial prophylaxis is also advocated for patients considered to be particularly liable to infectious complications, such as the elderly ones with chronic low-grade infections of the urinary or respiratory tract, patients under treatment with adrenocortical steroids and those exposed to extensive radiation. All agree on the indication for prophylactic antibiotics during operations or manipulations in the oral cavity and the genitourinary tract in patients with rheumatic or congenital heart disease in order to prevent bacterial endocarditis; this aspect has been reviewed in the earlier section I (11).

It is interesting, however, that controlled studies have failed to demonstrate any advantage of routine use of antibiotics in some of the situations in which it has been generally considered to be indicated. It may be helpful, therefore, to review some of the recent reports of studies on chemoprophylaxis in various types of surgery.

OBSTETRICS

It was the striking effectiveness of the first sulfonamide, Prontosil, in the treatment of hemolytic streptococcal puerperal sepsis that really launched the modern era of antimicrobial therapy. It was to be expected, therefore, that antibacterial agents would be used extensively in the treatment and prophylaxis of infections complicating childbirth. Well-controlled studies of the efficacy of these agents are, however, few, and most of them were reported several years ago. Streptococcal infections have become uncommon in obstetric and other hospital practice and infections with antibiotic-resistant organisms are more frequent, so that the current status of antibacterial agents is difficult to evaluate on the basis of these older reports.

Early in 1946, Power and Cravotta (12), after a survey of the use of penicillin in obstetrics, concluded that prophylactic administration following rupture of the membranes or inertial labor and in potentially infected patients "has not failed to assure a smooth convalescence and has shortened the period of hospitalization. Following cesaerean section, especially in infected and potentially infected cases, the margin of safety is

undoubtedly increased. . . ." In a larger and controlled study, Pierce (13) in 1948 reported 2.3% morbidity due to genital tract infections in several hundred women treated with a vaginal suppository of 200,000 units of penicillin immediately after delivery, as compared with 5.3% among controls and even higher figures in the preceding 10 years. He considered this usage to be of particular value in early rupture of membranes, protracted labor and genital tract infections; the amount of nursing care and the number of hospital days and of genital infections were reduced. In another large series, Tupper and Davis (14), using what would now be considered small doses, e.g., 20,000 units of penicillin immediately post partum and every 3 hours for 10 days, recorded a reduction to 2.2% in standard morbidity from 7.4% in the previous year when penicillin was not used. There were fewer fevers, early and late, and the morbidity during operative procedures was less, the reduction being mostly in the genital infections. "Sapremia" was reduced from 12 to 6% and the average hospital stay was also shortened, but there was no difference in the incidence of mastitis.

Controlled studies of vaginal cultures during the puerperium indicated that it was possible to disinfect the uterus in most women by the administration of various doses of penicillin (15) or of chlortetracycline, 2.0 Gm. per day (16). Most of the organisms recovered during penicillin therapy were nonpathogens, and the only penicillin-sensitive organisms were cultured more than 48 hours after the use of small doses. A reduction in maternal infections was achieved with chlortetracycline.

Keetel and co-workers (17, 18) reported on the effect of prophylactic penicillin in 2 successive series of deliveries with concomitant controls. In both instances, there was a reduction in incidence of the puerperal fevers, particularly those of 2 or more days' duration, but the infant mortality was unaffected. They concluded that there was no reason for prophylaxis in normal women, but that it should be used under conditions that predispose to infection (18). From experience with small groups of patients given penicillin with or without streptomycin, Hesseltine and Kephart (19) concluded that such treatment had no proved value as routine practice but was probably useful in selected cases under close management, presumably by providing early therapy in such conditions. In a controlled study of 100 patients with premature rupture of membranes and prolonged labor given penicillin at regular intervals before delivery, Siddall (20) observed considerable protection against

puerperal infection, but this was far from complete and there appeared to be no advantage to the child. In 228 patients with various complications of pregnancy Posner *et al.* (21) used tetracycline (2 Gm. in 4 doses orally or 1 Gm. in 2 doses intravenously daily); "the results, with few exceptions, were remarkable," and there were few side effects, usually minor. They considered tetracycline to be ideal for prophylaxis and treatment of obstetric infections.

Unfortunately, more recent experiences in general hospitals and during the many outbreaks of infections in nurseries indicate that staphylococci and other organisms resistant to penicillin, the tetracyclines and other antibiotics are the major cause of infections in hospitals today (22); and this is probably true in lying-in hospitals as well. Studies of prophylaxis with antibiotics in these circumstances are urgently needed to determine their current value. The controlled studies of Kass on the prevention of pyelonephritis in pregnancy and possibly of prematurity and perinatal death by treatment of asymptomatic bacteriuria during pregnancy indicate that properly directed and controlled chemoprophylaxis may have an important place. These studies are considered later in the section on the urinary tract.

SEPSIS IN GENERAL SURGERY

Although antibacterial agents came into use as a routine measure for the prevention of postoperative sepsis in this and many other countries after World War II, there are few controlled observations from which the value of such prophylaxis can be judged. The kind of experience that encouraged this practice is represented by the report of Griffin *et al.* (23) on the prophylactic chemotherapy of appendicitis. They observed 108 cases at Cook County Hospital during a 7-month period in 1947. The mortality in these cases, in which penicillin and sulfadiazine were used routinely after appendectomy, was 0.9%, in contrast with previous rates (in larger numbers of cases) of 4.3% in 1944–1945, 3.9% in 1937–1938 and 7.6% in 1928–1932. These authors inferred that the morbidity and period of hospitalization were also reduced by the therapy. Although this was termed a preliminary report, there seems to have been no follow-up publication with additional data.

In 1954, McKittrick and Wheelock (24) reviewed the complications of elective surgery on the gallbladder and bile ducts

at the Massachusetts General Hospital and could not demonstrate any benefit from the routine use of antibiotics. Indeed, there were more postoperative infections and fevers in those who had received an antibiotic than among comparable patients who had not. A later review by B. A. Barnes *et al.* (25) of 1,947 herniorrhaphies and hysterectomies performed at the same hospital indicated that, when similar risks were compared, there was no evidence that the systemic use of antibiotics either increased or decreased the risk of sepsis. Linder (4) in 1957, reported to the Royal Society of Medicine that, in his experience in Berlin, wound infections and pulmonary complications after gastric operations were slightly more frequent in patients given antibiotics. Hasslinger (quoted by Taylor (8)) reported a large series of gastrectomies in which he observed a greater incidence of local and chest complications in patients who had been given sulfonamides and antibiotics than in those not so treated.

Howe (26) in 1956 reported a steady rise in surgical wound infections at the Massachusetts Memorial Hospital up to 1954; this was followed by both a significant lowering of the carrier rates of penicillin-resistant staphylococci and a 50% reduction of postoperative wound infections after the institution of a relatively simple program for prevention of cross-infection and judicious use of antibiotics. His experience suggested that the routine use of antibiotics prophylactically was more harmful than beneficial. Subsequently, in a summary of his own experience and that of others, Howe (6) stated:

> When prophylactic antibiotic therapy is directed against mixed gram-positive and gram-negative organisms, there is a risk that a resistant organism will emerge to predominance . . . especially if broad spectrum therapy is prolonged. A new and less favorable bacteriological problem may thus be created. The surgeon is usually dealing with such a polybacterial flora when he prescribes prophylactic antibiotics and the danger of setting the stage for staphylococcal complications is a real one. . . . The indications for prophylaxis in surgery are shrinking as experience accumulates.

Similar experiences were reported by Adams (3) and by Harris (27), both of whom reduced the incidence of wound infections significantly by improving the protection of wounds against direct and indirect contamination in the operating room and the discontinuance of routine antibiotic prophylaxis. Wolma and Lynch (28) also concluded from their experience with postoperative infections that antibiotics should be used only when evidence of infection exists. They observed that it has

never been proved that prophylactic antibiotic therapy prevents infections, but it has been demonstrated that they hasten the emergence of antibiotic-resistant strains of organisms.

From Columbus, O., J. Barnes *et al.* (29) reported that routine injection in the recovery room of 600,000 units of benzathine penicillin and 0.5 Gm. of dihydrostreptomycin in 449 patients did not reduce the incidence of postoperative infections (11.4%) below the incidence (9.8%) in 558 control patients not given antibiotics. The prophylactic therapy, however, did predispose to the emergence of penicillin- and streptomycin-resistant bacteria which were found in 76% of strains from treated patients and in 22% from controls. Another controlled study of the routine use of penicillin and streptomycin after clean operations was reported by Sanchez-Ubeda *et al.* (30). The prevalence of infectious complications was not affected, but there was an increase of infections with penicillin-resistant staphylococci in the hospital. These workers also cautioned against introducing prophylaxis with other antibiotics until there is clear-cut evidence that the general surgical patient will benefit from it.

Postoperative Pulmonary Complications

Hoerr (31) found the incidence of pulmonary complications following elective operations on the upper abdomen to be identical in patients treated with therapeutic doses of penicillin and in those not given antibiotics. He considered that penicillin was not effective when used alone for prophylaxis, that prophylaxis should be directed against the mechanical factors leading to atelectasis and that penicillin should be used only when infection occurred in the unexpanded lung.

MISCELLANEOUS "CLEAN" SURGERY

Elek and Conen (32) demonstrated that the pathogenicity and virulence of a small inoculum of Staphylococcus aureus in a fresh wound of a volunteer were greatly enhanced by the presence of a silk suture acting as a foreign body. When a suture was not left in the skin, as many as 7,000,000 staphylococci were needed to induce a minimal pus-producing lesion. With a suture in place, as few as 300 organisms of the same strain and under similar conditions produced fever, systemic

symptoms and a severe local infection requiring incision and drainage. In one subject, the addition of chlortetracycline prevented the development of the suppurative lesion, suggesting that multiplication of the organism is also required.

Using this lead, Echeverria and Olivares (33) incorporated chlortetracycline or neomycin in the sutures during operations by dipping the sutures in solutions of the antibiotics and found that the reaction along the suture line was thus improved. This requires further confirmation under controlled conditions and with various antibiotics and bacterial strains, particularly in view of the recent observations by Weaver and Middlebrook (34). They found that an experimental wound infection with a penicillin-resistant staphylococcus could be prevented in rabbits by the administration of procaine penicillin, provided the inoculum was small enough. This protection was lost if the staphylococcus put into the wound had been exposed to penicillin before the inoculation. These workers concluded that penicillin should be kept out of the environment wherever penicillin-resistant staphylococci are prevalent. They did not test the use of tetracycline in a similar manner with tetracycline-resistant staphylococci.

These observations of Weaver and Middlebrook are also of interest in relation to the routine use of penicillin in wounds following closure of the fascia, as formerly employed by Caswell *et al.* (35). This procedure was, however, accompanied by numerous other environmental control measures and resulted in a precipitous drop in the incidence of wound infection. Subsequently, Caswell (36) questioned the value of the routine topical use of penicillin prophylactically in wounds. He believed that antibiotic prophylaxis might be limited to situations in which there was an epidemic of staphylococcal wound infections, and then used only for a limited time, employing for this purpose such agents as neomycin and bacitracin to which the epidemic strain was susceptible.

Moderately high concentrations of most antibiotics are well tolerated in the skin and probably do not interfere with wound healing. In guinea-pigs, Sergeant *et al.* (37) tested various tetracyclines, chloramphenicol, neomycin and polymyxin B in 3% ointments applied to fresh experimental wounds. Only chlortetracycline retarded the healing time of the wounds.

HERNIORRHAPHY.—Three recent comparisons of infections following herniorrhaphy with and without chemoprophylaxis are worth mentioning. The report of B. A. Barnes *et al.* (38)

from the Massachusetts General Hospital covered the years 1937–1957. It included 273 patients who had full doses of an antibacterial agent before and for at least 4 days after the operation and 1,295 others not given such therapy; infections occurred in 3.3% of the former and 4.1% of the latter. Eisenman (39) noted no difference in the infection rate in 400 consecutive herniorrhaphies in which antibacterial prophylaxis had been used and in 400 others in which it had not been used. He termed this type of prophylaxis "an odious practice." Finally, Myers (40) collected the case records of both simple and complicated herniorrhaphies from 24 community hospitals in 7 states. He found that the use of antibiotics prophylactically varied from 7 to 100% in different hospitals. Infection occurred in 4.0% of 496 patients in whom antibiotics were used but in only 1.3% of 943 untreated patients. From a study of these cases he concluded that 74% of all the patients received the drugs *needlessly*, for an average of 5.1 days and at an average cost of $44.50 exclusive of the nursing time required for their administration.

HYSTERECTOMY.—B. A. Barnes *et al.* (38) also compared results following hysterectomy, with and without prophylactic antibacterial agents given routinely in the manner described for herniorrhaphy. Infections occurred in 3.8% of 920 prophylactically treated patients and in 3.5% of 4,273 patients operated on without such therapy.

ORTHOPEDIC SURGERY.—Tachdjian and Compere (41) reviewed the records of 3,000 consecutive clean cases of major orthopedic operations performed on private patients by 7 attending surgeons of 1 hospital between January 1952 and June 1957. Major infections followed 1.89% of 1,900 operations in which antibiotics were prescribed as a routine, and in only 0.74% of 1,100 operations in which they were not used at all. Antibiotics were used successfully to treat 6 of the 8 infections that occurred in patients who had not received them prophylactically, whereas most of the infections in the prophylactic group were due to penicillin-resistant staphylococci. The authors concluded that the routine use of antibiotics in orthopedic surgery is unwise.

ARTERIAL PROSTHESES.—Infection is a major source of failure of the synthetic arterial prostheses (42). Although the prosthesis may retain its function during infection or without soft-tissue cover, it acts as a foreign body hindering the control of the infection and the attempt to cover it. Persistence of infection may

necessitate removal of the prosthesis and construction of a new channel or the sacrifice of a limb. Prophylactic antibiotic therapy has therefore been recommended, in addition to strict asepsis (8, 9, 42), but there is no evidence that infection has been prevented by its use in such cases.

BRAIN SURGERY.—Because of the danger and seriousness of introducing infection during long operations on the brain, prophylactic antibiotic therapy is often recommended (1, 8, 9). Nonirritating agents are required for topical, intraventricular or intracerebral use, and bacitracin has been found useful for that purpose (43). The optimal agents and methods are not well worked out, nor is the extent of the protection afforded. There is great need for data on infections developing during or soon after "clean" operations involving the brain and spinal cord with and without the use of antibiotics.

CARDIAC SURGERY.—This was discussed in a previous issue in relation to the prevention of bacterial endocarditis (11).

HEMORRHAGIC SHOCK

Fine and his co-workers (44–47) have evolved the concept that endogenous bacteria and their toxic products play an important role in irreversible hemorrhagic shock. In their hands, the mortality in animals in which such shock is induced experimentally has been conspicuously reduced by the administration of antibiotics intravenously or orally. Chlortetracycline, oxytetracycline and neomycin have been the most effective for this purpose, but they fail to protect if administration is delayed until after transfusions have failed to restore circulation. In their dogs, Clostridia are commonly found in the tissues but rarely in the blood during life; they are found in both after death, and other intestinal bacteria are also found in about one fourth of the animals (46). Similar protection is afforded to animals with experimental fecal peritonitis by administration of antibiotics before the onset of hypovolemic shock (47).

The value of the prophylactic use of antibiotics in patients with extensive hemorrhage before or soon after shock develops has not been clarified, but the premise on which the procedure is based has been questioned by other workers. Thus, Hardy *et al.* (48) found no evidence of a bacterial factor in their experiments on dogs, although the animals given chlortetracycline did show a greater reduction in the number of positive blood

cultures. They suspect that antibiotics may have limited application. Downie (49), who has produced a standard type of hemorrhagic shock with bleeding into the jejunum and ileum of rats, was unable to show any reduction in mortality or in the extent of the hemorrhage by pretreatment of the animals with chlortetracycline. Moreover, McNulty and Linares (50), using germ-free animals, found that bacteria and bacterial products are not essential to the development of irreversibility in hemorrhagic shock.

A resolution of this problem, especially with respect to the value of antibiotics in patients with extensive hemorrhage, is obviously important, particularly in view of the fact that antibiotic therapy itself is exceedingly difficult to manage once shock has developed to a point where renal function is impaired (51). The need for early and appropriate antibacterial therapy of peritonitis before shock develops is understandable.

THORACIC SURGERY

Patients in whom operations are carried out through contaminated areas of the lung should receive antimicrobial agents which are active against the organisms that have been found or are expected to be present (8, 52, 53). Eriksen *et al.* (53) found that postoperative administration of routine doses of penicillin, penicillin plus streptomycin or chlortetracycline gave rise to totally resistant bacteria, especially Staph. aureus, and was associated with a high incidence of postoperative empyema. They obtained better control by the use of "large" doses of penicillin (500,000–2,000,000 units twice daily), which were effective against "totally resistant" strains of staphylococci. They reported a reduction in the number of complications and also in the number of resistant staphylococci in personnel and materials on their wards.

Other investigators have not had the same experience even when large doses of penicillin were used routinely. Blowers *et al.* (54) reported that infections of wounds and intrathoracic spaces with penicillin-resistant Staph. aureus became so common that in 1952 it became necessary to close the thoracic surgery unit. Correction of faulty procedures reduced infection rates from 11 to 4% and the Staph. aureus carrier rates from 74 to 37%, but this later rose to 62%. Before 1952, all major operations were done under an "umbrella" of penicillin from

the day before operation to recovery or at least for 10 days postoperatively. After 1948, streptomycin was included for the treatment of possible tuberculosis. After 1952, the routine use of penicillin for "clean" cases was abandoned and antibiotics were used only when the bronchus was divided. Established pyogenic infections were treated with appropriate agents. Griffiths (55) also reported that the routine use of penicillin failed to prevent postoperative chest infections.

Therapy with antituberculous agents is indicated in resectional surgery for tuberculosis. Late reactivation of pulmonary tuberculosis is less frequent (6 or 7%) in patients who have received therapy with more than 1 antituberculosis drug for 6 months or longer before the operation than in those treated for 1 month or less (17%). The early postoperative mortality is not affected by the duration of previous treatment (56).

Tubercle bacilli with varying degrees of resistance are often present in open cavities that have failed to heal under prolonged chemotherapy. With resection in such cases, it may be desirable to use some of the less common antituberculous drugs, although isoniazid in large doses appears to have some protective effect even when organisms resistant to it are present. Cycloserine, viomycin, pyrazinamide and kanamycin are available for this purpose, but there is not enough reliable information on their efficacy in these circumstances. The antimycobacterial action of tetracycline is inadequate for this purpose, and large doses are not tolerated well enough to be used.

SURGERY OF THE BOWEL

Bacteriologic studies of the stomach and duodenum at the time of operation have shown that they are usually free from bacteria in ulcer patients, but pathogenic organisms, mostly Escherichia coli, are usually found in the stomach when cancer is present (4, 57). In this instance, preoperative administration of oxytetracycline usually reduced or cleared the bacteria up to the day of operation but did not prevent an abundant growth as early as the day after operation. The flora was altered, however, and resistant pathogens were then found which caused difficulties in the postoperative treatment of bacterial complications (57, 58). Wound infections in 1 clinic were somewhat more frequent and more severe after partial gastrectomy when

antibiotics (penicillin plus streptomycin) were used routinely postoperatively than when they were not used (4).

Campos *et al.* (59) found that the normal intestinal flora is altered by the oral administration of tetracycline, there being an overgrowth of aerobes, mostly coliforms and Proteus, a reduction of sporulating anaerobes and rapid emergence of resistant strains. Anlyan *et al.* (60), however, reported a reduction in the bacterial counts but no marked change in the flora by tetracycline in doses up to 750 mg. every 6 hours for 48 hours. On the other hand, neomycin, 1 Gm. every 6 hours for 72 hours, inhibited almost the entire intestinal flora and appeared to be a safe and satisfactory preoperative preparation for operations on the colon and rectum. Side effects were similar from both drugs, consisting mostly of nausea and occasionally of vomiting.

The longest experience with the use of antibacterial agents for bowel surgery is that of Poth (61, 62). By 1953, after 12 years of using various absorbable and nonabsorbable agents, Poth (61) recommended neomycin in combination with sulfathalidine for intestinal antisepsis and urged that neomycin be reserved for this purpose only, in order to minimize the possibility of resistant organisms emerging. His regimen also includes a low residue diet, bowel cleaning by purgation with castor oil and enemas, decompression of the bowel before or at operation and placing of the antibiotic into the lumen of the bowel at operation. In 1957, Poth (62) again reviewed his experience and concluded that the danger from spillage had practically disappeared. He also stressed the need for preserving the blood supply and felt that parenteral administration of antibiotics was unnecessary except as added protection against ischemic necrosis.

In 1958, Cohn (63) reviewed his studies on antibiotics in colon surgery done mostly with Longacre, over several years. He had studied some 28 antibacterial agents which he put into 3 groups: (1) not recommended—all single absorbable chemicals and antibiotics; (2) satisfactory—neomycin alone or in combination with oxytetracycline or chlorquinaldol; and (3) recommended—(*a*) for special use, neomycin with erythromycin, novobiocin, ristocetin or tetracycline, and (*b*) for general use, in combination with neomycin, either amphotericin or nystatin, bacitracin or polymyxin B, sulfathalidine or thiostrepton. These are combined with a cleansing regimen as recommended by Poth and used for 72 hours. In addition, Cohn places the antibiotics into the bowel at operation and continues

their use in lower and less frequent doses through a plastic tube for 5 days.

A comparison of the incidence of complications and deaths at the Mayo Clinic following the preoperative use of a tetracycline alone orally or a combination of penicillin, streptomycin and dihydrostreptomycin parenterally revealed no difference except that the tetracyclines were superior when intraperitoneal anastomosis was involved (64). Dearing (65) reviewed investigations of various antibacterial agents and concluded that their use before operation is desirable but that there is no ideal agent. He recommended neomycin and tetracycline for 36 hours before surgery and bacitracin postoperatively as soon as fluids are tolerated. He advised against the use of erythromycin, novobiocin or oleandomycin preoperatively so that they might be reserved for specific purposes, particularly against resistant staphylococci. He would not recommend nystatin, feeling that the harmful role of the intestinal yeasts that appear during the short-term antibiotic regimens is not established. Sulfonamides are considered ineffective, streptomycin and chloramphenicol too erratic in their effects, and tetracyclines too likely to be followed by staphylococcal enteritis to warrant their use. Above all, Dearing emphasized that the antibacterial agents are not a substitute for sound surgical judgment and good surgical aseptic technic.

It is of interest that Tyson and Spaulding (66), after several years of intensive studies, decided to abandon the use of antibiotic agents in bowel procedures not complicated by either significant obstruction or occlusive arteriosclerotic vascular disease or when extensive surgery was not anticipated, their advantages not often enough outweighing the disadvantages. They had encountered neomycin-resistant organisms in feces and considered this a good reason for limiting its use, and they felt the same way about antibiotics in general. They were also concerned about staphylococcal enteritis due to resistant strains.

Above an obstruction, the small intestine contains a profuse growth of fecal flora, and the longer the obstruction, the more proximal this flora extends. Below the obstruction the contents are sterile or flora is scant. The peritoneum remains sterile as long as the bowel remains viable (67). In experimental strangulation of the small bowel with obstruction and ischemic damage, Cohn (68) found that antibiotics facilitate recovery and help maintain the viability of the segment by preventing infection which otherwise tends to destroy the ischemic area. This

has been confirmed by Barnett and Messina (69) and the therapy has been effective in human cases (63).

Neomycin and tetracycline have been recommended by Schatten (70) for use intraperitoneally at the time of operation for acute bacterial peritonitis and continued through polyethylene catheters up to 72 hours postoperatively. Neomycin is preferable for this purpose, but its use may result in rapid onset of respiratory arrest that may prove fatal (71). This is due to a neuromuscular blocking effect which potentiates that of the anesthetic and may in turn be relieved by neostigmine (72). Streptomycin and kanamycin may also do this, but this complication apparently does not occur if the intraperitoneal instillations are begun after the effect of the anesthetic has worn off (73) and if moderate doses are used (74).

CONTAMINATED WOUNDS, TETANUS AND GAS GANGRENE

Experiences with battle casualties in World War II indicated that prophylactic administration of penicillin was useful in the management of contaminated wounds. Henneberg (75) summarized the consensus that antibiotics offer a valuable 6 hours of grace by delaying the development of infection and permitting more effective debridement. In Korea, clostridial infections were not a major problem because of the immediate response to adequate surgery and the continuous use of antibiotics which were made possible by the tactical conditions of a stationary front (76). Many of these Korean wounds were examined within 8 hours; about 44% of them yielded pathogenic Clostridia on culture at the time of debridement, but only 0.08% developed gas gangrene (76, 77). In a similar series of wounds treated in India during World War II, clostridial myositis developed in about 1.5% of cases, and during World War I the incidence was 5%; the mortality from this infection in the two World Wars was about 30%, but there were no deaths from it in Korea (76).

Experimental studies in animals may shed some light on the value of prophylactic antibiotic therapy in infected wounds. In 1949, Novak *et al.* (78) were able to show a remarkable reduction of mortality in mice infected with lethal doses of detoxified spores of Clostridium tetani (injected with calcium chloride) by the prophylactic use of procaine penicillin in 2% aluminum monostearate. The development of symptoms and

death were also delayed. The same dose was more effective when injected into the necrotic area than in some other site. Delay in the administration of the penicillin resulted in increased mortality. Penicillin was much more effective than antitoxin, but the combination was most effective and was recommended for use in human beings (79).

Anwar and Turner (79a) studied the effects of various antibiotics on tetanus organisms in vitro and their effects with and without antitoxin in experimental infections of mice, hamsters and rabbits. Only penicillin proved sporicidal but only at a concentration of 100,000 units in suspensions containing 2,000,000 spores per ml. and after incubation at 37 C, not at 4 C. They found no significant difference in the effectiveness of penicillin, tetracycline or erythromycin in mice. The protective effect of penicillin and oxytetracycline was considerably reduced if administration was delayed for 24 hours. Antitoxin alone afforded only temporary protection; but when given with oxytetracycline 24 hours after infection, tetanus did not develop. They concluded that penicillin and the tetracyclines are bactericidal in vitro and in vivo on vegetative forms and offer the best protection when given in doses comparable to those used in clinical cases; they are, therefore, the prophylactic agents of choice in previously unimmunized individuals.

The combination of penicillin and polyvalent antitoxin was more effective than penicillin alone against infection with Cl. histolyticum, but not with Cl. bifermentans or Cl. novyi (80). It is essential to maintain inhibitory tissue levels with procaine penicillin to achieve the greatest reduction in mortality (80). Garrod (81) found the tetracyclines and penicillin to be the most effective antibiotics against various species of Clostridia in vitro and advocated the use of penicillin for the prevention and treatment of gas gangrene in battle wounds.

In experimental massive traumatic wounds in goats, Mansberger *et al.* (82) were able to demonstrate that prophylactic antibiotic therapy prolonged survival and that all of the agents used, except neomycin orally and dehydrostreptomycin intramuscularly, were more effective for this purpose than only replacement of blood. Broad-spectrum antibiotics were more effective than those of limited spectrum. Indefinite survival followed the administration of blood and antibiotics immediately after the wounding, provided debridement was done within 4–6 hours. The wounds in penicillin-treated animals showed a marked depression in bacterial counts lasting 6 hours; there-

after the organisms grew rapidly, approximating control levels at 18 hours after injury, at which time the spatial extent of infection did not differ in penicillin-treated and untreated animals (83).

Sanford *et al.* (84) studied the effect of early use of penicillin and oxytetracycline intramuscularly for contaminated traumatic soft-tissue wounds in rabbits. In nondebrided wounds, local infection was not prevented; but the period of its development was prolonged by such treatment, and systemic toxemia, bacteremia and death were decreased if the wound was contaminated with organisms that were sensitive in vitro. Large doses, however, had little if any effect if the organisms were resistant. Sublethal doses of total body x-radiation did not affect the results. In other experiments, Howes (85) obtained no effect with systemically administered antibiotics but could prevent infection of experimental crushed wounds when he used them locally in concentrations that were adequate but not injurious to tissues; he still advocates and uses topical antibiotic therapy in all wounds.

BURNS

The surface of a thermal wound is virtually sterile at inception but rapidly becomes infected by a variety of common bacteria in most instances. During and after World War II, many studies were made on the effects of antibacterial prophylaxis on the course of burns, particularly on the protection against infection, with observations on the bacterial flora and on the subsequent success of skin grafts. Personal experiences with the use of sulfadiazine systemically in severe respiratory and surface burns indicated that infection of deep burns was not prevented and usually occurred after the first week (86). Staphylococcus aureus was the most common organism in these burns, but hemolytic streptococci were sometimes present. Infections were about as frequent in these cases as in similar ones treated at another hospital at the same time with much stricter asepsis and with topical use of penicillin in low concentrations in some cases (87). The sulfonamides were probably responsible for minimizing pulmonary infections and for preventing many deaths from pneumonia. The results of the most extensive and continuous studies, however, have been reported from the Burns Unit of the Birmingham (England) Accident Hospital, and

some of them have been reviewed at different times (88–91), most recently by Taylor (8).

The hemolytic streptococcus still appears to play an important role in the delay of healing and the failure of skin grafts. Penicillin applied in the form of a cream (1,000 units per Gm.) has reduced the incidence of this organism markedly but not completely, and reactions to such treatment have been relatively uncommon (about 0.5%) (92). Systemic treatment with penicillin, however, has failed to prevent colonization by hemolytic streptococci in spite of their remaining highly sensitive to it, presumably because the relatively low levels attained in the burned wound are rendered ineffective by the penicillinase-producing bacteria (especially staphylococci) that proliferate there (90). In addition, strains of hemolytic streptococci resistant to tetracycline and erythromycin have emerged during systemic treatment with these antibiotics (90). Considerable effort has also been made to prevent cross-infection by careful dressing technics and elaborate environmental controls, with partial success in reducing the incidence of streptococci; these procedures did not prevent colonization of the burn by strains of Staphylococcus, Pseudomonas and Proteus, which still is a serious problem (88).

Chemoprophylaxis against the last-mentioned organisms has proved disappointing. Initial successes in reducing the staphylococci by systemically administered tetracyclines or erythromycin were followed by the rapid emergence of resistant strains and subsequent failure to control the organisms. Lowbury (90) demonstrated clearly that the incidence of staphylococci resistant to these agents is directly related to the frequency with which they are used. Gibson and Thompson (93) showed that the incidence of chloramphenicol-resistant staphylococci also increases rapidly in a burns ward where this agent is used extensively. The use of combined therapy in attempts to prevent emergence of resistant variants has not always proved satisfactory (90). A trial of the combination of erythromycin and novobiocin, in spite of its early therapeutic effectiveness, proved disappointing because 20% of double-resistant staphylococci appeared after it was used for 3 months. Staphylococci resistant to neomycin, bacitracin and chlorhexidine dihydrochloride (Hibitane) were not encountered, however, and the incorporation of some of them with penicillin into ointments applied topically significantly reduced the frequency of implantation of antibiotic-resistant staphylococci.

Infection with Pseudomonas aeruginosa is particularly undesirable in burns because of its destructive effects on the skin. This organism emerged as an important invader during the use of penicillin ointment (94). It was possible to reduce the occurrence of this organism, but not to eliminate it regularly from the burns, by applying an ointment of polymyxin E topically. Resistant strains of Pseudomonas did not emerge, but the polymyxin E was too expensive and so was reserved for the therapy of contaminated burns in which skin grafting was contemplated (8). Polymyxin B or colistin should be equally effective and should not be too costly if used in low but still effective concentrations and for brief periods in areas where Pseudomonas is frequently encountered.

Taylor (8) summarized current concepts as follows: Local application of penicillin (in lanette wax) is desirable and successful for prevention of invasion by hemolytic streptococci. Systemically administered antibiotics fail to prevent colonization with staphylococci because of the ready emergence of resistant strains. Rigorous control of cross-infection must remain the chief protection against infection with staphylococci and other common invaders, notably Pseudomonas; but these too may be controlled by the local application of neomycin, bacitracin and polymyxin. These drugs are too costly for routine use but may be indicated in large burns in which early and successful grafting is mandatory. Lowbury (90) expressed the view that perhaps the use of antibiotics in rotation and with economy might prove more effective than combined therapy. He sees the greatest hope for the antibacterials in the development of agents which, like bacitracin, neomycin, chlorhexidine and vancomycin against Staphylococcus and the polymyxins against Pseudomonas, never or hardly ever select variants that are resistant and still capable of causing infection. There is no satisfactory local or systemic chemoprophylaxis against Proteus and some other gram-negative bacilli (91). Until such agents are available, he feels that the best procedure is to improve aseptic discipline and to block the lines of bacterial contamination, as was indicated by the earlier studies of Colebrook *et al.* (88).

A controlled study of the topical use of several antibacterial agents, singly and in combination, in granulating burn wounds in relation to skin grafting was reported by Hummel *et al.* (95) from the Brooke Army Medical Center. They used nitrofurazone, chloramphenicol, tetracycline, neomycin, polymyxin B and also petrolatum alone, and treated burns only before the

60th day. Judging by the percentage of graft "takes," appearance of the granulating tissues and bacterial counts from the surface, these workers obtained no evidence that one agent was more effective than any other or that any was superior to the petrolatum base alone. They concluded that locally applied antibiotics have no more value than frequent cleansing and changing of the dressings in preparation of the recipient site in the well-treated burn patients. They did not, however, study chronically infected burns.

URINARY TRACT

In 1946, Prince (96) reported what he considered to be the first instance of prevention of infection following transurethral resection of the prostate. In 17 of 36 patients given sulfadiazine on the day before and penicillin plus sulfadiazine for 5–7 days after this operation, the urine was sterile at the time of discharge from the hospital; the other 19 patients, in 10 of whom the preoperative urine was sterile, had infected urine when discharged, the most frequently cultured organism being Pseudomonas, though some yielded Escherichia coli, Aerobacter and staphylococci. Blahey (96a) in 1952 reported the results of studies with oxytetracycline (chosen because of the high concentrations excreted in the urine) given before and after gynecologic operations. He concluded that, although pyuria was reduced in treated patients who did not have urinary retention, infection was not reduced; only the bacterial flora of the urine was changed. Whereas E. coli predominated in preoperative urines, these organisms were rarely found postoperatively; on the other hand, Proteus and staphylococci, which were rare in preoperative urines, predominated after the operations and made difficult problems in management.

In 1954, Jönsson and Erlanson (97) concluded after study of several hundred cases that chemotherapy did little to prevent infection following surgery for prostatic disease or tumors of the bladder where an indwelling catheter or suprapubic drainage was necessary. On the other hand, patients operated on because of calculi or malformations seldom became infected. Repeated catheterization or other instrumentation and indwelling catheters nearly always led to infection with resistant strains that were nosocomial in origin. In the treatment of established infections of the urinary tract, they, like others, obtained good

results in nearly all acute, uncomplicated cases, but only in about a third of the chronic and complicated ones.

From his review of urinary tract infections in 1955, Kass (98) concluded that the prophylactic use of antibacterial drugs, singly or in combination, in patients with inlying catheters is probably valueless, serving merely to convert the urinary flora from susceptible to resistant strains. Pierce (99), in 1958, after similar experiences, adopted the policy of postponing the use of antibacterial agents until 6 weeks after prostatectomy. He cited Volk as indicating that nitrofurantoin, like other antibacterial drugs, had failed to prevent urinary infections following vaginal operations in patients with indwelling catheters. Lunt *et al.* (100) also noted that catheterization accounted for 25% of infections following gynecologic operations despite antimicrobial therapy.

The prophylactic use of chloramphenicol pre- and postoperatively in a carefully alternated series of 100 cases of transurethral resection of the prostate was reported by Appleton and Waisbren (101). The drug had no significant effect, as judged by the occurrence of postoperative bacteremia, urine cultures, pyuria, drainage period, fever, period of hospitalization and mortality. These workers found no evidence to justify the use of prophylaxis in such cases. In a study of patients with retropubic prostatectomy, Marshall (101a) found that those who present with an infected urine after a brief period of catheter drainage appear to get better results if treated with an appropriate antibiotic than if given either "routine" prophylactic antibiotics or none; sterile cases, on the other hand, do very well without antimicrobial prophylaxis.

Patients with malfunction or paralysis of the bladder requiring drainage by catheter present another situation in which prophylactic chemotherapy appears to be logical but in practice is futile. Riley and Knight (102) observed 50 consecutive patients with paralytic poliomyelitis with this complication; 44 of them had indolent, persistent and steadily progressive infection, although often without symptoms. Bladder catheterization and immobilization of the patients were the predisposing factors. The frequent use of antibacterial drugs in these patients led to a predominance of strains of Proteus and Aerobacter in the urine, and calculi developed in 21 of the 44 infected patients.

That preconceptions and vain hopes, rather than hard established facts, still prevail in this field is well illustrated in Nourse's discussion (103) of the management of the patient

who fails to void after operation. He emphasized the great care required in catheterizing such patients in order to minimize infection and prefers a properly applied indwelling catheter to repeated catheterization when required because of the overdistended bladder, which should be avoided at all times. Referring to chemoprophylaxis, he stated: "Evidence points to the futility of chemoprophylaxis in preventing infection. . . . I personally will continue to use maintenance doses of some drug even if it does nothing but salve my conscience. The clinical well-being of the patient is important."

The question that may properly be asked is how the well-being of the individual patient, and also of all other patients, may best be promoted. Added care to prevent or minimize the introduction of new infection, as, for example, by a thoroughly closed and bacteria-proof system of drainage, is most important, but other methods, perhaps more physiologic and potentially less harmful than the use of antibacterial drugs, must be sought. The proper use of acidifying agents (104), increased urine flow and intermittent drainage (105), which decrease retention of urine and provide a less favorable milieu for rapid bacterial growth, may provide more reasonable methods of minimizing the extent of the infections and the resulting tissue reactions.

There is, however, one related area in which prophylactic chemotherapy seems to be highly useful, namely, pyelonephritis of pregnancy (106). A systematic study of quantitative bacterial counts of the urine of women during pregnancy has revealed significant asymptomatic bacteriuria (100,000 colonies or more per ml.) in about 6–8%. Follow-up of these patients indicated that 40% of these women, when untreated, develop acute pyelonephritis either later in pregnancy or soon after delivery. Elimination of the bacteriuria by the prophylactic administration of a sulfonamide or other active drug continuously during the pregnancy prevented the occurrence of such infections in every instance. More recent evidence suggests the possibility that reduction of prematurity and perinatal deaths may be expected from such prophylaxis (107).

The addition of neomycin to the contrast medium used in retrograde pyelography did not prevent the occurrence of bacteremia, and additional antibacterial therapy was required in some cases (108).

The subject of urinary tract infections should not be dismissed without some caution as to the interpretation of cultures of the urine. The urine is an excellent medium for many com-

mon intestinal and other bacteria, and small numbers of contaminating organisms will grow out readily if the urine is permitted to stand or if cultures are made in a liquid medium. Only quantitative cultures and direct smears of properly collected, clean-voided specimens of patients not receiving bacteriostatic drugs can provide reliable evidence of a relation of the cultured organisms to possible infection. Treatment or prophylaxis based merely on the finding of organisms and on tests of their susceptibility to antibiotics has resulted in a tremendous waste of therapy and unnecessary harmful effects in many patients.

SPECIAL CONTAMINATED AREAS

SEPTIC HAND.—Infections of the hand may be of considerable importance, especially to workers kept off their jobs for long periods. Although the use of antibiotics to aid in localizing such infections is generally recommended, their value after surgical drainage is controversial. The conflicting evidence was reviewed by Anderson (109), who also studied 357 cases divided into 3 unselected groups receiving no chemotherapy or penicillin orally or intramuscularly. The average respective healing times was 9.4, 9.5 and 9.2 days. He therefore concluded that the routine postoperative use of penicillin in such cases can be safely omitted provided careful surgical technic, based on accurate anatomic diagnosis, is used. Possibly web abscess and threatened infection of the structures that move or support the hand are proper indications for chemotherapy.

DOG BITES.—These may have special significance because Pasteurella septica (P. multocida) is common in the respiratory tract of dogs (and cats). Reports of infection with this organism are few; this, according to Lee and Buhr (110), may be due to inadequate culturing, and actually such infections may be quite common and serious. They were able to demonstrate this organism in 12 (17%) of 69 dog bites. The strains tested have all been moderately sensitive to penicillin (inhibited by 0.2 units or less per ml.) and they are readily eradicated from the respiratory tract of dogs by penicillin therapy. Frank wound infections developed in 29% of all of the bites and in 47% of 30 that had been sutured, but only in 1 of 9 patients who had received prophylactic penicillin. Of the 12 bites that yielded P. septica, 10 became infected; these required prolonged treatment and

resulted in unsightly scars. Since many children are bitten by dogs, often on the face, these authors recommend prophylactic penicillin therapy for all patients with serious dog bites, especially those which are sutured, to assure healing with a minimum of scarring.

ORAL SURGERY.—The uses of antibiotics in all types of oral surgery were reviewed by Alling and Pulaski (10). They noted that the most rewarding response to antibiotic therapy has followed its judicious use to supplement appropriate surgery in acute infections, such as periapical, parietal and pericoronal abscess, ulceromembranous stomatitis, acute osteomyelitis and infections and cellulitis of the contiguous facial spaces. They recommended starting treatment in such cases immediately, while awaiting results of bacteriologic studies, then altering the antibiotics as indicated. Chronic infections involving necrotic bone, marginal gingivitis, pericoronal flaps, papillary hyperplasia of oral mucosa and periapical granulomas do not respond well to antibiotics. Routine extraction of teeth, most minor surgery (such as root resection), surgery for immediate dentures, biopsies, and excision of cysts and tumors do not require antibiotic therapy if the mouth is otherwise healthy. Prophylaxis during such procedures is, however, recommended in patients with congenital or valvular heart disease, as noted previously (Finland [11]).

Alling and Pulaski (10) recommended the routine use of antibiotics in operations involving resections, grafts, fractures of the maxilla or mandible. Whenever maxillofacial surgery is complicated by craniocerebral involvement or surgery includes entry into accessory nasal sinuses or the cranial cavity, a sulfonamide and/or chloramphenicol should be used to protect against meningitis. They believe that antibiotics have extended the latitude of possible surgical procedures and have reduced the morbidity after surgery. Unfortunately, there are no controlled studies which permit comparisons of results of routine prophylactic use of antibiotics with the effect of their prompt use specifically directed against infectious complications as soon as they are detected.

The incorporation of penicillin into dentifrices has been suggested as a possible way to prevent dental caries. However, controlled studies failed to bear this out clearly. The proportion of the less sensitive organisms of the normal mouth flora increases during continuous use of such dentifrices, but highly resistant strains do not appear (111).

ANORECTAL SURGERY.—Wounds in the anorectal areas are obviously exposed to the large variety of bacteria of the fecal flora. Although it would seem that prophylaxis with antibacterial drugs should be helpful in surgery of this area by inhibiting multiplication of these organisms, preventing infection and thus aiding healing, the possibility of eliminating sensitive organisms and permitting resistant ones to multiply introduces a serious hazard. Banov (112) has reported a group of cases of hemorrhoidectomy and fissurectomy, all performed by the same operator, in which some patients received no antibiotics and others received erythromycin or tetracycline beginning within 4 hours after the operation and continuing for the next 3–7 days. No difference could be detected objectively in the healing of the wounds in the 3 groups. McGivney, discussing these findings, indicated that he had had similar results with broad-spectrum antibiotics in similar cases and also noted that even preoperative preparation of the bowel with neomycin and sulfathalidine made little difference in the appearance and healing time of the wounds as compared with controls. He feels that the use of antibiotics in anorectal surgery is not only impractical but may be dangerous.

GENERAL DISCUSSION AND SUMMARY

In 1950, before the New York Academy of Medicine, this writer (113) reviewed the prophylactic uses of antibiotics that had been found of value and noted others for which there was no adequate basis in any controlled clinical or epidemiologic experience. It was then noted, in summary, how many uses could be, and indeed had been, rationalized to the point where continuous administration of antibacterial agents could be justified for almost any individual, literally "from the womb to the tomb." In the present issue and in the preceding parts of this series (11, 114) an attempt was made to gather some of the relevant reports from which the value of chemoprophylaxis for a variety of conditions could be assessed. Some of these reports represent the results of genuine attempts to arrive at a true assessment of the use of the antibacterial agents by objective data from well-designed and well-controlled studies. Others represent observations that are less well controlled and the results are, therefore, less conclusive; and in some areas, only opinions based on impressions or testimonials from uncontrolled experi-

ence are available. Some of the early impressions of favorable effects have not withstood the test of time, and even the introduction and use of new drugs as they became available have resulted in only temporarily improved effects, after which their advantage was also lost.

It should be clear, from the studies cited, that only by use of these drugs under strictly controlled conditions will a reliable estimate of the benefits emerge, and then possibly only in those particular circumstances because of changing conditions. Some of the major factors that determine the feasibility and probable effectiveness of antibacterial prophylaxis of infections may be summarized briefly.

THE ORGANISM.—Since the antimicrobial drugs act only by killing or inhibiting the growth of bacteria, prophylaxis can be successful only if the organism causing the infection to be prevented is susceptible to the drug that is used and can be eliminated from the individual or prevented from implanting and multiplying at its site of entry. This is best attained when a single organism is involved and is highly sensitive. In addition, the durability of the organism, its prevalence and reservoirs in the individual and in the environment are important with respect to the possibilities of its elimination and then of reinfection. When multiple organisms are involved, the chances of success diminish according to the degree of resistance of the various pathogens to the drug or drugs used and the interactions of the organisms in the presence of the drugs. For example, large numbers of penicillinase-producing staphylococci or other organisms may interfere with the action of penicillin on streptococci in the throat; and the elimination or reduction in numbers of the common species of organisms from the bowel flora by tetracyclines or neomycin may encourage the multiplication of resistant enteropathogenic staphylococci or of Candida. The rate at which the organism is killed by the drug used and its tendency to acquire resistance to that drug, as well as the nature of that resistance, whether temporary or durable, in the strains carried by the individual or found in his environment, are also determinants of the immediate and long-term success of the prophylaxis.

LOCATION OF THE ORGANISM.—The site of the infection or of the implantation of the pathogen may be important in determining the mode of application and dosage and even the drug of choice.

THE ANTIBACTERIAL AGENT.—The absorption, excretion and

disposition of the prophylactic drug, its penetration into various body tissues, its binding to protein, susceptibility to antagonistic actions of other agents or inactivation by bacterial products (penicillinase, sulfonamide inhibitors) and the effect of changes in pH on its action are all important determinants of the choice of agent to be used, its mode of administration and the probability of its success. Regardless of how favorable all of these factors and the activity of the drug may be, its toxicity by the method of administration chosen may be the overriding factor.

DURATION AND INTENSITY OF TREATMENT.—These vary with the purpose of the prophylaxis. If the protection is directed against a single exposure with a highly susceptible organism that is easily eradicated, as in gonorrhea, a single small or moderate dose may be adequate, or only a short course may be necessary, as in exposure to meningococcal infection. However, if the protection desired is against frequent or possibly continuous exposure or against chronic infection with an organism or infection that is only very slowly reduced or controlled, treatment must be continuous and prolonged and may have to be intensive. If it is essential to prevent reinfection that may occur at any time, as in the case of streptococcal infections in rheumatic subjects or infection by pneumococci or H. influenzae, as in chronic bronchitis, the prophylaxis must also be continuous.

HOST FACTORS.—In certain infections, factors in the host may interfere with the success of chemoprophylaxis. These may include the intracellular character of the infectious agent, as in viral or rickettsial diseases, or inaccessibility to the action of the drug of bacteria in a walled-off location, or the bacteriostatic nature of the drug action that precludes eradication of the organisms, or other reasons that are less clear. In such circumstances, long-term or preferably intermittent therapy may be effective, presumably because of the improvement of host resistance during the intervals between the treatment periods and before infection has increased to serious proportions.

INDIVIDUAL VS. MASS PROPHYLAXIS.—Continuous prophylaxis in an individual is most likely to be effective with a minimal risk of infections with resistant variants if carried out on an ambulatory basis or in the home, that is, removed from an environment where large amounts of antibiotics are used and in which the opportunities for cross-infection with antibiotic-resistant organisms are great, namely, the hospital. Mass prophylaxis has the best chance for success if it is relatively brief, the causative organism of the infection to be prevented is highly

susceptible to the antibiotic used and resistant pathogens are not prevalent at the time. The success of prophylaxis in hospitals, institutions or large compact units may be limited by the emergence or introduction and spread of resistant, pathogenic and invasive variants, as was the case during the program of mass sulfadiazine prophylaxis in the Armed Services during World War II, or during attempts to prevent the spread of epidemic staphylococcal infections in nurseries, or to minimize such infections in surgical wounds or burn surfaces. The emergence of increasing proportions of strains of organisms highly resistant to the widely used antibiotics (115), particularly among staphylococci and the common coliform organisms, has been the most important complication of the widespread use of antibiotics, especially for prophylaxis (22). It has also been, in turn, the determining factor in the diminishing effectiveness of chemoprophylaxis and thus indirectly a cause of increased morbidity from its use because the resulting infections, even when not more numerous, are more difficult to control.

In general, when an antibacterial agent is to be used in the prophylaxis of infections that may develop in contaminated wounds or during operations through a contaminated field, it is advisable to obtain suitable cultures of the area before treatment is instituted and to repeat these cultures during the course of therapy, which can then be changed or adjusted as indicated by the results of the cultures and sensitivity tests if the condition of the patient or of the wounds suggests that the infection is not adequately controlled. Mere growth of organisms, especially in small numbers without evidence of infection, should not in itself be an indication for institution or change of therapy.

Nearly all competent surgeons and others interested in surgical infections seem to agree that the routine use of antibacterials for prophylaxis, especially in clean operations, is unnecessary and undesirable (1–9, 116–119). Its routine use is a confession of insecurity for some, and may act as a license for partial laxity, or at least as a deterrent to maximal effort to obtain the optimum of control by strict asepsis. In a sense, therefore, such prophylaxis represents a reversion, in part, to the older era of antisepsis in surgery.

As more and better-controlled studies reveal increasing numbers of situations in which the advantages of routine prophylaxis are more than balanced by their disadvantages, reliance placed on antibacterials is decreasing, and more emphasis is being placed on skilful surgery and strict asepsis, with adequate

control of the environment. Antibiotic prophylaxis in surgery may thus be considered another phase of the "struggle against sepsis" (119). Antibiotics in general are likely to be applied most successfully when used specifically for infection with organisms against which they have proved to be effective. In surgery, their optimal use is as an adjunct to surgical evacuation of suppurative foci and in the prevention of extension or invasion from an active, acute inflammatory lesion.

REFERENCES

1. Meleney, F. L.: Present status of antibiotics in surgery, S. Clin. North America 36:275, April, 1956.
2. Altemeier, W. A.: Current evaluation of the antibiotics in surgery, Postgrad. Med. 20:319, October, 1956.
3. Adams, R.: Prevention of infection in surgical wounds, New England J. Med. 256:625, Apr. 4, 1957.
4. Linder, F.: Discussion of the problem of the resistant organism and chemotherapeutic sensitivity in surgery, Proc. Roy. Soc. Med. 50: 153, May, 1957.
5. Foster, F. P., Deitch, B., and Dadez, J. L.: Antibiotics in surgery: Some general principles and practical points, S. Clin. North America 37:811, June, 1957.
6. Howe, C. W.: Staphylococcal Disease on Surgical Services, in Burney, *et al.* (118), pp. 75-92.
7. Pulaski, E. J.: Discriminate antibiotic prophylaxis in elective surgery, Surg., Gynec. & Obst. 108:385, April, 1959.
8. Taylor, G. W.: Preventive use of antibiotics in surgery, Brit. M. Bull. 16:51, January, 1960.
9. Barber, M., Dutton, A. A. C., Beard, M. A., Elmer, P. C., and Williams, R.: Reversal of antibiotic resistance in hospital staphylococcal infection, Brit. M. J. 1:1, Jan. 2, 1960.
10. Alling, C. C., and Pulaski, E. J.: Current trends in antibiotics in oral surgery, Oral Surg. 12:743, June, 1959.
11. Finland, M.: Chemoprophylaxis of Infectious Diseases: I. General Considerations and Application to Streptococcal Infections, Rheumatic Fever, Glomerulonephritis and Bacterial Endocarditis, DISEASE-A-MONTH, December, 1959.
12. Power, H. A., and Cravotta, C. A.: Penicillin in obstetrics: Final report, Pennsylvania M. J. 49:401, January, 1946.
13. Pierce, R. R.: Penicillin vaginal suppositories in prevention of postpartum morbidity, Am. J. Obst. & Gynec. 55:313, February, 1948.
14. Tupper, W. R. C., and Davis, M. M.: Prophylactic use of penicillin in obstetrics, Am. J. Obst. & Gynec. 57:569, March, 1949.
15. Guilbeau, J. A., Schaub, I. G., and Andrews, M. S.: Penicillin ther-

apy in the obstetrical patient, Am. J. Obst. & Gynec. 58:101, July, 1949.
16. Guilbeau, J. A., Schoenbach, E. B., Schaub, I. G., and Latham, D. V.: Aureomycin in obstetrics: Therapy and prophylaxis, J.A.M.A. 143:520, June 10, 1950.
17. Keetel, W. C., Scott, J. W., and Plass, E. D.: Evaluation of prophylactic penicillin administration to parturient women, Am. J. Obst. & Gynec. 58:335, August, 1949.
18. Keetel, W. C., and Plass, E. D.: Prophylactic administration of penicillin to obstetric patients, J.A.M.A. 142:324, Feb. 4, 1950.
19. Hesseltine, H. C., and Kephart, S. B.: Prophylactic use of penicillin and streptomycin in certain obstetric conditions, Am. J. Obst. & Gynec. 59:184, January, 1950.
20. Siddall, R. S.: Prophylactic penicillin during labor in infection-prone patients, Am. J. Obst. & Gynec. 60:1281, December, 1950.
21. Posner, A. C., Konicoff, N. G., and Prigot, A.: Tetracycline in obstetric infection, Antibiotics Annual, 1955–1956, pp. 345–348.
22. Finland, M., Jones, W. F., Jr., and Barnes, M. W.: Occurrence of serious bacterial infections since introduction of antibacterial agents, J.A.M.A. 170:2188, Aug. 29, 1959.
23. Griffin, W. D., Silverstein, J., Hardt, H. G., and Seed, L.: Prophylactic chemotherapy in appendicitis, J.A.M.A. 133:907, Mar. 29, 1947.
24. McKittrick, L. S., and Wheelock, F. C.: Routine use of antibiotics in elective surgery, Surg., Gynec. & Obst. 99:376, September, 1954.
25. Barnes, B. A., Behringer, G. E., Wheelock, F. C., and Wilkins, E. W., Jr.: Surgical sepsis: Impression and facts, Surgery 46:247, July, 1959.
26. Howe, C. W.: Prevention and control of postoperative wound infections owing to Staphylococcus aureus, New England J. Med. 255: 787, Oct. 25, 1956.
27. Harris, R. J.: Staphylococcus wound infection, Texas S. J. Med. 55: 886, November, 1959.
28. Wolma, F. J., Jr., and Lynch, J. B.: Postoperative complications due to Staphylococcus aureus, Surgery 45:796, May, 1959.
29. Barnes, J., Pace, W. G., Trump, D. S., and Ellison, E. H.: Prophylactic postoperative antibiotics: Controlled study of 1,007 cases, A.M.A. Arch. Surg. 79:190, August, 1959.
30. Sanchez-Ubeda, R., Fernand, E., and Rousselot, L. M.: Complication rate in general surgical care: Value of penicillin and streptomycin as postoperative prophylaxis—study of 511 cases, New England J. Med. 259:1045, Nov. 27, 1958.
31. Hoerr, S. O.: Antibiotics and prevention of postoperative pulmonary complications, Ohio M. J. 45:225, March, 1949.
32. Elek, S. D., and Conen, P. E.: Virulence of Staphylococcus pyogenes for man: Study of problems of wound infection, Brit. J. Exper. Path. 38:573, December, 1957.

33. Echeverria, E., and Olivares, J.: Clinical and experimental evaluation of suture materials treated with antibiotics, Am. J. Surg. 98:695, November, 1959.
34. Weaver, J. K., and Middlebrook, G.: Experimental prophylaxis of staphylococcal infection in rabbits, Proc. Soc. Exper. Biol. & Med. 103:108, January, 1960.
35. Caswell, H. T., *et al.*: Bacteriologic and clinical experiences and methods of control of hospital infections due to antibiotic resistant staphylococci, Surg., Gynec. & Obst. 106:1, January, 1958.
36. Caswell, H. T.: Discussion of "Staphylococcal Disease on Surgical Services, in Burney *et al.* (118), pp. 93–97.
37. Sergeant, C. K., Pouka, J. L., and Brush, B. E.: Effect of antibacterial agents on clean wounds, Arch. Surg. 78:480, March, 1959.
38. Barnes, B. A., Behringer, S. E., Wheelock, F. C., Jr., and Wilkins, E. W., Jr.: Analysis of factors associated with sepsis in two operative procedures, 1937–1957, New England J. Med. 261:1351, Dec. 31, 1959.
39. Eisenman, B.: Discussion of Barnes *et al.* (25).
40. Myers, R. S.: Misuse of antibacterials in inguinal herniorraphy, Surg., Gynec. & Obst. 108:721, June, 1959.
41. Tachdjian, M. O., and Compere, E. L.: Postoperative wound infections in orthopedic surgery, J. Internat. Coll. Surgeons 28:797, December, 1957.
42. Schramel, R. J., and Creech, C., Jr.: Effects of infection and exposure on synthetic arterial prostheses, A.M.A. Arch. Surg. 78:271, February, 1959.
43. Teng, P. M., and Meleney, F. L.: Treatment of intracranial suppuration with reference to local and systemic use of bacitracin, Surgery 33:321, March, 1953.
44. Fine, J.: Effect of peripheral vascular collapse on antibacterial defense mechanisms, Ann. New York Acad. Sc. 66:329, Oct. 5, 1956.
45. Schweinburg, F. B., Frank, H. A., and Fine, J.: Bacterial factors in experimental hemorrhagic shock: Evidence for development of a bacterial factor which accounts for irreversibility to transfusion and for loss of the normal capacity to destroy bacteria, Am. J. Physiol. 179:532, November, 1954.
46. Jacobs, S., *et al.*: Bacterial action in development of irreversibility to transfusion in hemorrhagic shock in the dog, Am. J. Physiol. 179: 523, December, 1954.
47. Frank, E. D., *et al.*: Effect of antibiotics on hemodynamics of hypovolemic septic shock, Am. J. Physiol. 182:166, 1955.
48. Hardy, E. G., *et al.*: Studies on role of bacteria in irreversible hemorrhagic shock in dogs, Ann. Surg. 139:282, March, 1954.
49. Downie, H. G.: Effect of Aureomycin on production of hemorrhagic shock in the rat, Canad. J. Biochem. & Physiol. 34:1119, November, 1956.

50. McNulty, W. P., Jr., and Linares, R.: Hemorrhagic shock of germfree rats, Am. J. Physiol. 198:141, January, 1960.
51. Kunin, C. M., and Finland, M.: Restrictions imposed on antibiotic therapy by renal failure, A.M.A. Arch. Int. Med. 104:1030, December, 1959.
52. Altemeier, W. A., Culbertson, W. R., and Vetto, M.: Prophylactic antibiotic therapy, A.M.A. Arch. Surg. 71:2, January, 1955 (editorial).
53. Eriksen, K. R., Hansen, J. L., and Lund, F.: Postoperative infection in surgery of the lung: Prophylaxis with high level systemic penicillin therapy, Acta chir. scandinav. 107:460, 1954.
54. Blowers, R., Mason, Y. A., Wallace, K. R., and Walton, M.: Control of wound infections in a thoracic surgery unit, Lancet 2:786, Oct. 15, 1955.
55. Griffiths, E.: Failure of penicillin to prevent postoperative chest infection, Brit. M. J. 1:803, Apr. 6, 1957.
56. Rayl, J. E., and Walkup, E.: Results of excisional surgery in the treatment of pulmonary tuberculosis, Tr. 17th Conf. of Chemother. of Tuberc. (Veterans Administration, Dept. of Medicine & Surgery, Washington, D.C.), pp. 225–232, February, 1958.
57. Högman, C. F., and Sahlin, O.: Infections complicating gastric surgery: 1. Bacterial flora of upper portion of alimentary tract and its response to antibiotics administered in connection with gastric surgery, Acta chir. scandinav. 112:271, 1956.
58. Sahlin, O., and Högman, C. F.: Infections complicating gastric surgery: II. Mechanisms of postoperative peritonitis, Acta chir. scandinav. 113:79, 1957.
59. Campos, J. V., *et al.*: Changes in intestinal flora under tetracycline, Gastroenterology 34:625, 1958.
60. Anlyan, W. G., Hart, D., Georgiade, N. G., and Poston, M. A.: Intestinal antisepsis with oxytetracycline (Terramycin) and neomycin: Comparative study, A.M.A. Arch. Surg. 68:28, January, 1954.
61. Poth, E. J.: Intestinal antisepsis in surgery, J.A.M.A. 153:516, Dec. 26, 1953.
62. Poth, E. J.: Critical analysis of intestinal antisepsis, J.A.M.A. 163: 1317, Apr. 13, 1957.
63. Cohn, I., Jr.: Antibiotics for colon surgery, Gastroenterology 35:583, December, 1958.
64. Phillips, D. F., Dearing, W. H., and Waugh, J. M.: Comparison of complications following intestinal surgery after oral and parenteral preoperative antibiotic preparation, Surg., Gynec. & Obst. 106:145, February, 1958.
65. Dearing, W. H.: Current status of preparation of intestine for operation: Critical appraisal, S. Clin. North America 39:1223, October, 1959.
66. Tyson, R. R., and Spaulding, E. H.: Should antibiotics be used in large bowel preparation? Surg., Gynec. & Obst. 108:623, May, 1959.

67. Bishop, R. F., and Allcock, E. A.: Bacterial flora of small intestine in acute intestinal obstruction, Brit. M. J. 1:766, Mar. 12, 1960.
68. Cohn, I., Jr.: Strangulation obstruction: Antibiotic protection, Surgery 39:630, April, 1956.
69. Barnett, W. O., and Messina, A. J.: Influence of massive antibiotics in experimental strangulation obstruction, Gastroenterology 36:534, April, 1959.
70. Schatten, W. E.: Intraperitoneal antibiotic administration in treatment of acute bacterial peritonitis, Surg., Gynec. & Obst. 102:339, March, 1956.
71. Doremus, W. P.: Respiratory arrest following intraperitoneal use of neomycin, Ann. Surg. 149:546, April, 1959.
72. Pittinger, C. B., and Long, J. P.: Potential dangers associated with antibiotic administration during anesthesia and surgery, A.M.A. Arch. Surg. 79:207, August, 1959.
73. Prigot, A., Shidlovsky, B. A., and Campbell, E. A.: Intraperitoneal use of kanamycin in therapy of established peritonitis and peritoneal contamination, Ann. New York Acad. Sc. 76:204, Sept. 30, 1958.
74. Greene, H. G.: Intraperitoneal neomycin in treatment of acute bacterial peritonitis, Surg., Gynec. & Obst. 107:169, August, 1958.
75. Henneberg, G.: Chemotherapie, Immunität und Prophylaxie, Antibiotica et Chemother. 2:91, 1955.
76. Howard, J. M., and Inui, F. K.: Clostridial myositis—gas gangrene: Observations of battle casualties in Korea, Surgery 36:1115, December, 1954.
77. Lindberg, R. B., Wetzler, T. F., Marshall, J. D., Newton, A., Stravitz, J. G., and Howard, J. H.: Bacterial flora of battle wounds at time of primary debridement: Study of Korean battle casualties, Ann. Surg. 141:369, March, 1955.
78. Novak, M., Goldin, M., and Taylor, W. I.: Tetanus prophylaxis with penicillin procaine G, Proc. Soc. Exper. Biol. & Med. 70:573, 1949.
79. Taylor, W. I., and Novak, M.: Prophylaxis of tetanus with penicillin, Ann. Surg. 133:44, January, 1951.
79a. Anwar, A. A., and Turner, T. B.: Antibiotics in experimental tetanus: In vitro and in vivo studies, Bull. Johns Hopkins Hosp. 98:85, February, 1956.
80. Taylor, W. I., and Novak, M.: Prophylaxis of experimental gas gangrene in mice, J. Bact. 61:571, May, 1951.
81. Garrod, L. P.: Chemoprophylaxis of gas gangrene, J. Roy. Army M. Corps 104:209, October, 1958.
82. Mansberger, A. R., Ochsner, E. W. A., Jr., Jacob, S., Oppenheimer, J. H., and Gillette, R. W.: Experimental shock from massive wounds: II. Evaluation of various therapeutic regimens with special reference to role of antibiotics, fluid replacement, and debridement, Surgery 43:708, May, 1958.
83. Oppenheimer, J. H., *et al.*: New preparation for study of experimental shock from massive wounds: IV. Effect of penicillin and

streptomycin on quantitative bacteriologic flora of the wound, Surgery 43:730, May, 1958.
84. Sanford, J. P., *et al.*: Experimental evaluation of usefulness of antibiotic agents in early management of contaminated traumatic soft tissue wounds, Surg., Gynec. & Obst. 105:5, July, 1957.
85. Howes, E. L.: Discussion of Barnes *et al.* (25).
86. Finland, M., Davidson, C. S., and Levenson, S. M.: Chemotherapy and control of infections among victims of the Cocoanut Grove disaster, Surg., Gynec. & Obst. 82:151, February, 1946.
87. Cope, O., *et al.*: Symposium on management of the Cocoanut Grove burns at Massachusetts General Hospital, Ann. Surg. 117:801, 1943.
88. Colebrook, L., Duncan, J. M., and Ross, W. P. A.: Control of infection in burns, Lancet 1:893, June 12, 1948.
89. Lowbury, E. J. L.: Cross-infection of wounds with antibiotic-resistant organisms, Brit. M. J. 1:985, Apr. 23, 1955.
90. Lowbury, E. J. L.: Hospital infection, Proc. Roy. Soc. Med. 51:807, October, 1958.
91. Lowbury, E. J. L.: Infection of burns, Brit. M. J. 1:994, Apr. 2, 1960.
92. Davies, M. R.: Penicillin sensitivity in patients with burns, Lancet 2:345, Aug. 16, 1958.
93. Gibson, C. D., Jr., and Thompson, W. C., Jr.: Response of burn wound staphylococci to alternating programs of antibiotic therapy, Antibiotics Annual, 1955–1956, pp. 32–34.
94. Jackson, D. M., Lowbury, E. J. L., and Topley, E.: Pseudomonas pyocyanea in burns: Its role as pathogen, and value of local polymyxin therapy, Lancet 2:137, July 28, 1951.
95. Hummel, R. P., Rivera, J. A., and Artz, C. P.: Evaluation of several antibiotics used locally on granulating wounds caused by thermal injury, Ann. Surg. 146:808, November, 1957.
96. Prince, C. L.: Prevention of urinary tract infection following transurethral prostate resection by combined use of sulfadiazine and penicillin, J. Urol. 56:121, July, 1946.
96a. Blahey, P.: Experiences with Terramycin in urinary and genital tract infections, Canad. M. A. J. 66:151, February, 1952.
97. Jönsson, G., and Erlanson, P.: Effect of chemotherapy and evaluation of sensitivity tests in vitro in surgical urinary infections, Acta chir. scandinav. 107:1, 1954.
98. Kass, E. H.: Chemotherapeutic and antibiotic drugs in management of infections of the urinary tract, Am. J. Med. 18:764, May, 1955.
99. Pierce, J. M.: Prophylactic use of antibiotics, Univ. Michigan M. Bull. 24:169, May, 1958.
100. Lunt, R. L., Dutton, W. A., Dewhurst, C. J., and Russell, C. S.: Incidence of infection following gynecological operations, Lancet 1:1240, June 15, 1957.
101. Appleton, D. M., and Waisbren, B. A.: Prophylactic use of chloramphenicol in transurethral resection of the prostate gland, J. Urol. 75:304, February, 1956.

101a. Marshall, A.: Prophylactic antimicrobial therapy in retropubic prostatectomy, Brit. J. Urol. 31:431, December, 1959.
102. Riley, H. D., and Knight, V.: Urinary tract infections in paralytic poliomyelitis, Medicine 37:281, December, 1958.
103. Nourse, M. H.: Management of patient who fails to void after operation, J.A.M.A. 171:1778, Nov. 28, 1959.
104. Kass, E. H.: Bacteriuria and diagnosis of infections of urinary tract, with observations on use of methionine as a urinary antiseptic, A.M.A. Arch. Int. Med. 100:709, November, 1957.
105. Kass, E. H., and Sossen, H. S.: Prevention of infection of urinary tract in presence of indwelling catheters: Description of electromechanical valve to provide intermittent drainage of the bladder, J.A.M.A. 169:1181, Mar. 14, 1959.
106. Kass, E. H.: Bacteriuria and pyelonephritis of pregnancy, Tr. A. Am. Physicians 72:257, 1959.
107. Kass, E. H.: Hormones and resistance to infection, Bact. Rev. 24: 177, March, 1960.
108. Hoffman, H. A., and de Carvalho, M. P.: Retrograde pyelography and use of contrast medium containing neomycin, J.A.M.A. 172:236, Jan. 16, 1960.
109. Anderson, J.: Dispensability of postoperative penicillin in septic hand surgery, Brit. M. J. 2:1569, Dec. 27, 1958.
110. Lee, M. L. H., and Buhr, A. J.: Dog bites and local infection with Pasteurella septica, Brit. M. J. 1:169, Jan. 16, 1960.
111. Zander, H. A.: Antibiotics in dentifrices, J. Am. Dent. A. 48:3, January, 1954.
112. Banov, L., Jr.: Postoperative use of antibiotics in anorectal wounds, South. M. J. 50:106, January, 1957.
113. Finland, M.: Present status of antibiotics in bacterial infections, Bull. New York Acad. Med. 27:199, April, 1951.
114. Finland, M.: Chemoprophylaxis of Infectious Diseases: II. Other Applications in Medicine and Pediatrics, DISEASE-A-MONTH, July, 1960.
115. Finland, M.: Emergence of antibiotic-resistant bacteria, New England J. Med. 353:909, Nov. 24; 969, Dec. 1; 1019, Dec. 8, 1955.
116. Kapp, D. F.: Antibiotic prophylaxis in unpredictable infections: A medical and surgical fallacy, Guthrie Clin. Bull. 26:165, April, 1957.
117. Jawetz, E., and Grossman, M.: Three ways to fight infection: Control of hospital infections requires: 1) reduction in number of organisms, 2) restriction of use of antibiotics, and 3) modification of patient's resistance, Mod. Hosp. 90:92, May, 1958.
118. Burney, L. E., *et al.*: *Hospital Acquired Staphylococcal Disease* (Proc. Nat. Conf., U.S.P.H.S. Communicable Disease Center and National Academy of Science–National Research Council, Atlanta, Ga., 1958), Summary Report of Discussion Groups.
119. Morton, J. J.: The struggle against sepsis, Yale J. Biol. & Med. 31: 397, June, 1959.

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